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Advanced medical interventions in pleural disease

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ABSTRACT The burden of a number of pleural diseases continues to increase internationally. Although many pleural procedures have historically been the domain of interventional radiologists or thoracic surgeons, in recent years, there has been a marked expansion in the techniques available to the pulmonologist. This has been due in part to both technological advancements and a greater recognition that pleural disease is an important subspecialty of respiratory medicine. This article summarises the important literature relating to a number of advanced pleural interventions, including medical thoracoscopy, the insertion and use of indwelling pleural catheters, pleural manometry, point-of-care thoracic ultrasound, and image-guided closed pleural biopsy. We also aim to inform the reader regarding the latest updates to more established procedures such as chemical pleurodesis, thoracentesis and the management of chest drains, drawing on contemporary data from recent randomised trials. Finally, we shall look to explore the challenges faced by those practicing pleural medicine, especially relating to training, as well as possible future directions for the use and expansion of advanced medical interventions in pleural disease.



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Technological advances and greater availability of techniques give a broad range of interventions for pleural disease <http://ow.ly/ZNYa2>

Introduction

The definition of an “advanced medical intervention” will undoubtedly be subject to debate and a great deal of geographical variation. Amongst respiratory physicians, the ability to perform simple pleural procedures

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has traditionally been a core requirement for both training and general practice, with more invasive techniques typically reserved for thoracic surgery or interventional radiology colleagues. Recent years have seen rapid and unprecedented improvements to both bedside medical technology and its availability to the general physician, leading to less distinction in which procedures are performed by which group. Coupled with an increasing recognition of pleural disease as an important and distinct subspecialty [1], and the rise of the “interventional pulmonologist”, tools such as thoroscopes, indwelling pleural catheters (IPCs) and point-of-care ultrasound are now increasingly commonplace in respiratory clinics worldwide [2]. The importance of this shift cannot be overstated: patients in many centres are now offered more rapid access to diagnosis and treatment [3], with yields and safety levels akin to those provided by other specialties [4, 5].

Rates of many common pleural diseases, such as malignant effusions and empyema, continue to increase [6–8]. For this reason, it is vital that knowledge of novel pleural techniques is disseminated as widely and as efficiently as possible. The aim of this review is therefore to bring the reader up to date with recent advances in the interventional aspects of pleural medicine, with as much focus as possible on what can be translated to usual, day-to-day practice. The following paragraphs will cover patient selection, medical thoracoscopy and pleural biopsy, temporary drainage procedures for both air and fluid, and how to optimise them, as well as the increasing role of ambulatory care and IPCs.

Patient selection

Appropriate patient selection is a necessary part of any investigative process. It is vital to ensure that any procedure offered to a patient is in their best interests, and not, as may be the temptation, simply because it is technically possible. Maintaining a clear and coherent dialogue with patients is key and this may require additional time be allotted to traditionally short consultations. A holistic assessment will entail a thorough exploration of the patient’s wishes, as well as their likely ability to cope physically with both the suggested investigation and any recovery period that may be required. In the case of ambulatory devices, such as IPCs or Heimlich valves, close consideration should also be made to a patient’s social and psychological context, especially as such devices may require help from family/other caregiver, and management over extended time periods. In addition, depending on the nature of the healthcare environment, the financial costs of an intervention both in the long and short term may have to be factored in when choosing the most appropriate management course.

From a practical point of view, assessing a patient as close to the date of a procedure as possible is likely to minimise the chances of an intervention needing to be cancelled. In the case of medical thoracoscopy especially, early patient assessment and ultrasound confirmation of fluid in the lateral decubitus position can be particularly beneficial, although some centres are now able to offer on-table alternatives to thoracoscopic biopsy if required [9]. Ultimately, the specifics of which patients are felt to be suitable for which procedures will be a local decision, factoring in centre facilities and operator experience alongside the patient aspects mentioned above.

Nonexpandable lung

The early identification of those with nonexpandable lung (NEL) is an important example of how robust patient selection can dramatically alter management pathways. To describe this phenomenon, the term “trapped” lung is often used interchangeably with lung “entrapment”. In general, both refer to the lung’s inability to expand normally into the pleural space, although it is perhaps more precise to recognise that that the two are actually distinct entities related to specific underlying pathologies [10]. NEL may be caused by central obstructing masses but is usually a result of either localised or generalised visceral pleural thickening, typically due to chronic inflammation caused by processes such as infection or pleural malignancy [10]. The presence of NEL and the lack of pleural apposition it causes significantly increase the chances of pleurodesis failure should this be attempted [11], meaning the early use of IPCs tends to be preferred in this setting [12]. It should be noted, however, that such recommendations are based upon relatively limited evidence and by no means guarantee symptomatic benefit for patients (figure 1) [14].

The dyspnoea associated with a pleural effusion is likely to be caused by disruption to the normally efficient mechanics of the inspiratory muscles and diaphragm [15, 16]; however, in the case of NEL, this may be relatively benign. Excessive fluid drainage in those with NEL can lead acutely to chest pain, distressing cough or a “pulling” sensation in the centre of the chest, although none of these are specific as they may also be associated with other situations, including re-expansion pulmonary oedema (REPO) [17]. Effusions related to NEL also tend to be rapidly recurrent, further supporting the use of IPCs in those with symptoms. Identification of NEL usually relies on post-procedure imaging revealing a hydropneumothorax, suggestive of a pneumothorax *ex vacuo*. This approach, however, requires an adequate fluid volume to be drained to reveal pathological areas. One study has suggested that, prior to invasive tests, advanced thoracic ultrasound techniques, such as M-mode and speckle tracing, may be applied to atelectatic lung in order to characterise its response to the cardiac impulse, potentially inferring the presence of NEL [19].

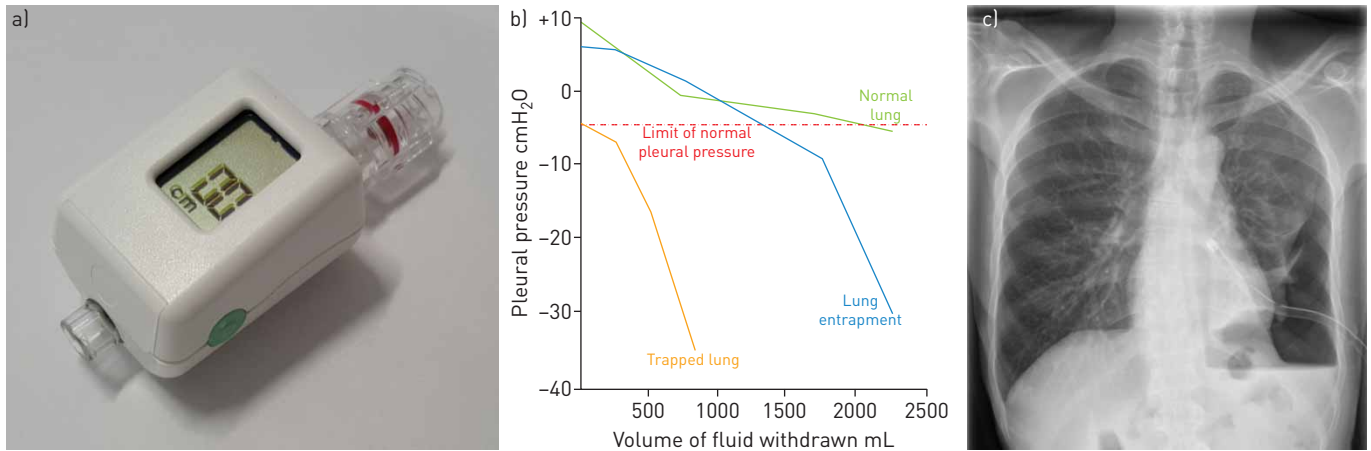


FIGURE 1 Nonexpandable lung. a) A single-use digital pleural manometer for use during thoracentesis. b) Pleural elastance curves representing normal, entrapped and trapped lung. Reproduced and modified from [13] with permission from the publisher. c) Chest radiograph demonstrating nonexpandable lung due to malignancy. A hydropneumothorax is visible at the left base with a large-bore chest drain *in situ* following thoracoscopy. The patient was treated with an indwelling pleural catheter.

More commonly, pleural manometry is advocated as a useful tool for characterising lung behaviour during fluid drainage. Despite there being a number of retrospective studies that have been unable to find a link between pressure readings and the development of chest discomfort [19], REPO [20] or pneumothorax *ex vacuo* [21], the possibility of being able to predict NEL is certainly attractive. There subsequently remains a select group of international practitioners who are strong campaigners for routine pleural manometry during thoracentesis [22, 23]. There are those, however, who remain unconvinced [24]. Historically, one of the likely limitations to the widespread adoption of manometry has been the relatively complicated equipment required, with a reduced chance that it will be available in the routine clinic setting. Furthermore, in order to derive the elastance curves needed to infer pleural behaviour, pressure readings will usually have to be taken at frequent intervals, potentially extending the time required to perform a procedure. Recent technological advances may be able to improve the availability of manometry with single-use, small, digital manometers, which have been shown to match measurements of more established methods [25]. Elsewhere, preliminary work has been conducted to evaluate continuous [26] and high-temporal resolution pressure measurement [27], both with encouraging results.

Short-term drainage procedures

For the majority of patients, the management of pleural fluid will entail either the insertion of an intercostal chest tube or therapeutic thoracentesis. Aside from the introduction of more refined equipment, such as dedicated pleural aspiration catheters, and a move towards the use of smaller chest tubes [28], recent years have seen little meaningful change in how these procedures are performed from a technical standpoint. Nonetheless, with the increasingly widespread adoption of thoracic ultrasound to provide real-time image guidance, it could be argued that this area has been at the forefront of the most important change in pleural interventional practice for a generation.

The optimisation of drain placement and aspiration site choice has been revolutionised by point of care thoracic ultrasound. Following evidence that serious harm was being done by performing procedures “blind” [29], national guidelines now state that image guidance should be seen as best practice [30]. The practicality of this is undoubtedly challenging to deliver, placing, as it does, additional strain on both pulmonology and radiology services [31]. In response, many countries’ training programmes have been adapted to ensure thoracic ultrasound is now part of the core skillset for junior pulmonologists [32–34]. The arguments for using ultrasound guidance during pleural procedures are compelling. A study performed over a decade ago was able to demonstrate that its use in comparison to clinically marked procedural sites allowed for both a greater success rate and a reduced risk of solid organ puncture, regardless of clinician seniority [35]. Such findings have been unequivocally backed up, both with meta-analysis data [36] and with a contemporary, 2-year retrospective cohort study of >60 000 procedures demonstrating a 19% reduction in the risk of pneumothorax when thoracentesis was performed with ultrasound guidance [37]. There are also those who advocate the use of ultrasound to locate and avoid the intercostal artery prior to pleural intervention (figure 2) [38].

In those patients who present with pneumothorax as their primary pathology or in those in whom a visceral puncture is suspected, the monitoring of air leak *via* an intercostal chest drain is of prime

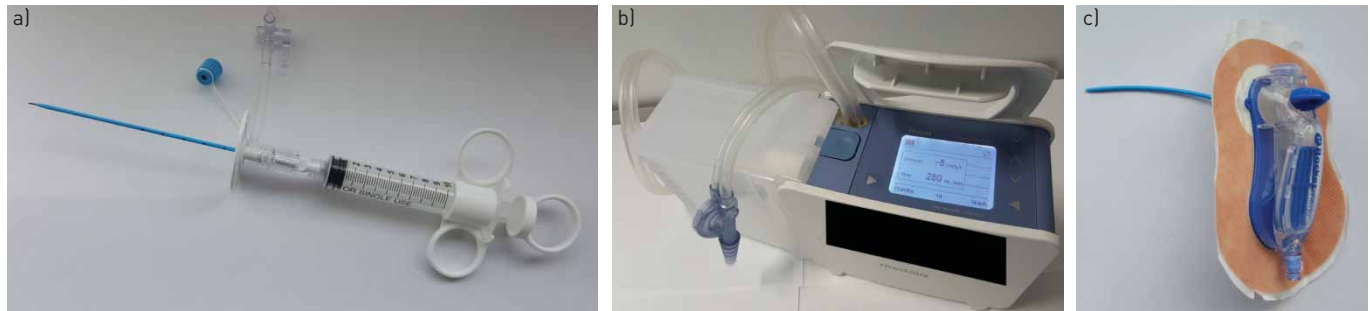


FIGURE 2 Examples of novel short-term drainage devices. a) 6-French thoracentesis catheter with integrated three-way tap. b) Chest drain bottle with integrated air leak monitor and digital suction. c) Pleural vent with integrated Heimlich valve for treatment of pneumothorax.

importance. Although initially targeted at post-thoracic surgical patients, chest drain bottles with digital air leak monitors are now increasingly available to the physician. The information they provide as to whether a leak is improving or persisting can guide further management with regards to the timing of drain removal or the need for surgical referral, respectively [39]. For some, especially those unfit for surgery with persistent secondary pneumothoraces or those looking to avoid hospital admission following a primary event, the use of a one-way (Heimlich) valve apparatus attached to a chest drain can allow greater freedom through ambulatory care [40]. New, transthoracic pleural vent devices designed for rapid and easy insertion have recently found their way to the market, with at least one randomised trial to test efficacy against standard care already in progress [41]. Using a similar study design, endobronchial one-way valves (which have been proven to be effective for the treatment of heterogeneous emphysema) [42] are also under investigation for the treatment of persistent pleural air leaks [43].

It is perhaps, however, the treatment of pleural effusions with chest drains that has seen the greatest advances in recent years. The Second Multi-Centre Intra-Pleural Sepsis Trial (MIST2), published in 2011, examined whether a combination of an intrapleural fibrinolytic (tissue plasminogen activator (t-PA)) with DNase could improve the radiographic appearances of those with pleural infection when compared to those treated with single agents or placebo [44]. The results confirmed the findings of MIST1, proving that single-agent fibrinolytic therapy had no role in this setting [45], but also demonstrated a 22% improvement in imaging appearances when dual-agent therapy was used instead of placebo. Of perhaps greater interest were the trial's secondary outcomes, which suggested a reduced surgical referral rate and reduced period of hospitalisation for those treated with the newer regimen [44]. Despite the combination group consisting of only 52 patients, there has been a great deal of enthusiasm amongst physicians for the use of t-PA/DNase; a recent retrospective series of 107 patients treated this way, drawn from around the world, suggested that even when used in a more pragmatic fashion than in the clinical trial setting, 92.3% of patients were able to avoid surgical intervention. Nonfatal bleeding was reported in <2%, although a fifth of patients required an increase in their analgesia due to chest pain [46].

The appeal of fibrinolytic treatment has also begun to extend beyond those with pleural infection. Patients with malignant pleural effusions (MPEs) are also susceptible to developing fluid septations and symptomatic loculations, a finding which can be particularly difficult to manage. A multicentre review of four pleural centres described 66 cases of fibrinolytic therapy given *via* an IPC for this indication. What was clear was that there is not yet a consensus on how, or indeed whether, treatment should be given to this population [47]. A recently reported randomised controlled trial (RCT), the TIME3 (Third Therapeutic Intervention in Malignant Effusion Trial) study, addressed whether treatment with urokinase *via* a chest drain could improve pleurodesis efficacy in loculated MPE. Although limited by under-recruitment, the results would suggest there is no benefit to this approach with respect to either patient symptoms or pleurodesis success (Eleanor Mishra and Najib Rahman, personal communication), further highlighting the need for prospective research to clarify the wider role of intrapleural fibrinolytic treatments.

Another controversy relating to MPE treatment has revolved around the theoretical interference of nonsteroidal anti-inflammatory drugs (NSAIDs) with the pleurodesis process [48]. Addressing both this and the most appropriate choice of drain size, the TIME1 study, a suitably powered, well-conducted RCT, has recently reported its findings [49]. In the trial, patients needing pleurodesis were allocated to receive either a 24-French (F) (large bore) drain or a 12F (standard small bore), in combination with either NSAID-based analgesia or a more typical opiate-based regimen. The results dispel the myth that NSAIDs have a detrimental effect on pleurodesis success but they were not found to be any better than standard opiate therapy. Perhaps more intriguingly, the study also found that those patients who had 12F drains suffered from a higher proportion of complications, including unintentional displacement, and concurrently

appeared to have a reduced chance of pleurodesis success, with 24F drains not necessarily causing greater discomfort to a clinically relevant degree [49]. These results appear to oppose the trend towards the increasing use of small-bore drains and certainly ensure the debate about whether drain size influences clinical outcomes will continue.

Despite studies such as this helping to inform the future use of chest drains, there are still a great deal of unanswered questions remaining. This means that areas such as whether or not to use pleural suction; when to give a pleurodesis agent; [50] and, indeed, what actually constitutes a successful pleurodesis remain largely unaddressed.

Indwelling pleural catheters

The increasing use of IPCs is another clear example of how technological advances in pleural medicine can have a direct impact on both the care of patients and the attitudes of physicians who manage them. Introduced in 1997, IPCs are now available routinely in much of the developed world, with a number of manufacturers having developed similar products. The core principle of all these devices remains the same: a tunnelled, silicone-based, multifenestrated chest tube is inserted into a pleural effusion, most commonly MPE, under local anaesthesia and in the outpatient setting. A proprietary valve connects the system to a dedicated fluid collection system, which is usually vacuum based. Patients and carers are empowered, therefore, to manage their recurrent collections at home and, in many cases, can avoid or significantly reduce hospital admissions [51–53]. Initially recommended for the management of those patients who had failed pleurodesis [12, 54] or those in whom trapped lung was the primary pathology [14, 55, 56], recent years have seen a shift in many centres towards an alternative paradigm, one in which IPCs are viewed as a valid first-line alternative to chemical sclerosant therapy [57, 58]. This idea was cemented by the publication of the TIME2 study, a multicentre RCT comparing standard chest drain and talc pleurodesis to IPC for the management of MPE. The patient-focused primary outcome of dyspnoea at 6 weeks was found to be no different between the two arms, with secondary analyses also suggesting those receiving an IPC spent less time in hospital and required fewer pleural procedures. In addition, subsequent analysis showed using an IPC was a more cost-effective strategy for those with a reduced life expectancy [59], a finding that has been replicated elsewhere [60–63]. These positive effects were balanced by a greater number of adverse events in the IPC group, although the rates of complications have been reported as significantly lower in larger, retrospective studies [64, 65]. Pleurodesis rates are also routinely lower in those patients treated with IPCs [64, 66], although many would argue this is not the desired effect of this treatment (table 1).

It has traditionally been felt that the use of chemotherapy precludes the insertion of an IPC due to a heightened possibility of infection. This idea has not been borne out by the literature, however, with numerous studies reporting no additional risk in this circumstance [71, 72]. In fact, as international experience with IPCs continues to grow, there is an increasing number of series describing their use in scenarios beyond MPE, including haemothorax [73], chronic empyema [74] and recurrent nonmalignant effusions [75]. This latter group of patients has recently been targeted due to the particularly high incidence of effusions associated with conditions such as cardiac and hepatic failure, or renal impairment [76–78]. Although current data are limited by numbers of patients and retrospective collection, it has been suggested that the use of IPCs in the benign setting is safe in sufficiently experienced hands, albeit with reduced pleurodesis rates compared to the MPE population [79]. A RCT is currently underway in the UK to clarify this further [80].

With the primary attractions of an IPC being ambulatory care and continuous access to the pleural space, it is not surprising that research has begun to emerge that describes these benefits applied in combination

TABLE 1 Indwelling pleural catheter (IPC) outcome data from series totalling more than 100 patients

First author [ref.]	Year	Total patients n	Empyema incidence %	Pleurodesis incidence %	Symptom improvement %	Duration of IPC days
VAN METER [64]	2010	1370	2.8	45.6	95.6	51
ROSENSTENGEL [67]	2012	1036	4.8	NA	NA	NA
SUZUKI [68]	2011	418	NA	26	91	44
MEKHAIEL [69]	2012	259	3.5	n/a	n/a	72
MULLON [70]	2011	109	4.6	59	96	90
		Total 3192	Mean 3.9	Mean 43.5	Mean 94.2	Mean 64.3

The series by VAN METER [64] is a meta-analysis of 19 smaller studies. NA: not applicable.

with more established treatments. A multicentre RCT exploring the outpatient administration of talc *via* an IPC is nearing completion [81], with one small series already reporting success locally using this approach [82]. Alternative pleurodesis agents, both established [83] and experimental [84] have also been administered this way, and some investigators have used them as a conduit for delivery of systemic compounds such as interferon- β or docetaxel [85, 86]. Animal studies have also suggested that pleurodesis agents may be coated onto IPCs to create drug-eluting catheters [87, 88]. The appeal of using IPCs in these ways is likely to drive further research, especially with the promise of increasingly individualised anticancer therapy.

A conversation regarding how they wish to have their recurrent effusion managed is one of the most important, yet simultaneously conceptually difficult, discussions a patient is likely to have with their pleural physician or surgeon. The idea that there may not be a “best” treatment (what suits one patient may not be appropriate for another, and what suits a patient at one time may not suit the same patient later in their care pathway) is particularly challenging for many. As more studies relating to the novel applications of IPCs are reported, navigating this complexity is likely to become an ever more crucial part of successful pleural medicine delivery.

Medical thoracoscopy and closed pleural biopsy

The incidence of pleural effusion is rising with over 1.5 million new cases diagnosed annually in the USA alone [30, 89]. Whilst the majority of these have a benign aetiology, it is estimated that >250 000 will be secondary to underlying malignancy [30, 90, 91]. This burden is likely to increase in the context of an ageing population and the growing number of individuals both newly diagnosed and surviving long-term with cancer as a result of widening options for oncological intervention. As MPE is frequently associated with poorer long-term outcomes [91], identifies patients with nonresectable disease in the setting of a distal primary cancer (including lung) and commonly results in significant disabling dyspnoea, the early identification of these patients is a clinical priority. Guidelines subsequently recommend a systematic approach to the investigation of a unilateral effusion of uncertain cause [30]. This process frequently culminates in the need to obtain diagnostic pleural tissue, either in the event of initial thoracentesis being unhelpful [92, 93] or, as is increasingly the case, additional material being required to facilitate histological and molecular analysis that will inform a patient’s continued management.

Interventional pulmonologists have two means by which to obtain diagnostic pleural tissue, closed pleural biopsy (CPB) or medical thoracoscopy. Neither of these techniques is new and both have drifted in and out of fashion over the years. However, while thoracoscopy is now widely acknowledged to be the gold standard, it is also recognised by the modern clinician advocating either one or both procedures that each has their advantages, disadvantages and place in the management of patients with pleural disease.

Closed pleural biopsy

CPB was first described by ABRAMS [94] and COPE [95] in the mid-20th century as an alternative means of obtaining pleural tissue without resorting to surgical thoracotomy. Its continued use more than five decades later can be attributed to factors including ease of use, low cost and tolerability to patients. This is of particular importance in parts of the world where access (financial and geographical) to healthcare resources is limited; this frequently coincides with those areas where tuberculosis is an important cause of pleural effusion and the diffuse nature of the infective pleuritis lends itself to CPB as a diagnostic strategy [96]. There has been technical progress nonetheless, notably a move towards core-cutting rather than traditional reverse bevel needles [97, 98], and the recognition that CPB should be performed using image guidance to optimise yield and patient safety [99, 100].

Image-guided CPB was initially the domain of specialist radiologists utilising either computed tomography (CT) or ultrasound to identify and sample localised pleural thickening and/or nodularity [99–102]. More recently though, and with thoracic ultrasound competencies being incorporated into pulmonology training programmes [32–34], this technique has been successfully adopted by physicians with a diagnostic yield comparable to that obtained by radiologists [9, 103]. The use of ultrasound guidance during CPB allows the operator to target areas of interest whilst compensating for respiratory movement in real time and avoiding the need for prolonged breath hold manoeuvres in potentially dyspnoeic patients. It has the further advantage of avoiding the exposure to ionising radiation required by CT or fluoroscopic guidance. The patient is placed in a lateral decubitus or, rarely, prone position and a low-frequency (2–5 MHz) curvilinear probe employed to direct the core-cutting biopsy needle, having first identified any underlying at-risk structures including intercostal vessels [38] and viscera. The technique permits, in expert hands, the sampling of not only pleural abnormalities but also chest wall and peripheral lung parenchymal lesions for diagnostic purposes [103, 104]. Whilst no formal guidelines exist, the authors would suggest performing between eight and 10 core pleural biopsies to ensure adequate sampling. Post-procedural ultrasound

assessment can also identify complications such as pneumothorax or intrapleural haemorrhage and, if necessary, allow early directed treatment (figure 3) [105].

CPB has the advantage of being a procedure that is well-tolerated by patients and easily delivered by clinicians without the need for a bespoke working environment, hospital admission or support team. As a minimally invasive approach, it has been advocated as a front-line initial diagnostic test alongside thoracentesis in the undiagnosed unilateral effusion; this might preclude the need for subsequent thoracoscopy and have particular value in those areas where tuberculosis is endemic [106, 107]. Whether this diagnostic benefit can be extrapolated to areas with a low incidence of tuberculosis is less clear [92] and needs further investigation in a modern-day pleural service. CPB also offers an alternative diagnostic approach in the patient either unwilling or too frail to have a thoracoscopic procedure, or indeed when a planned thoracoscopy itself fails [9]. Complication rates are low, with pain, bleeding and pneumothorax being seen in <5% of cases [9, 99, 103, 107]; this usually facilitates day-case management with a short period of observation post-procedure. Nonetheless, it is a purely diagnostic procedure and, unlike thoracoscopy, does not offer any therapeutic or symptomatic gain to the patient. The quantity of tissue that can be obtained by CPB is also limited by comparison with a thoracoscopic approach; this may

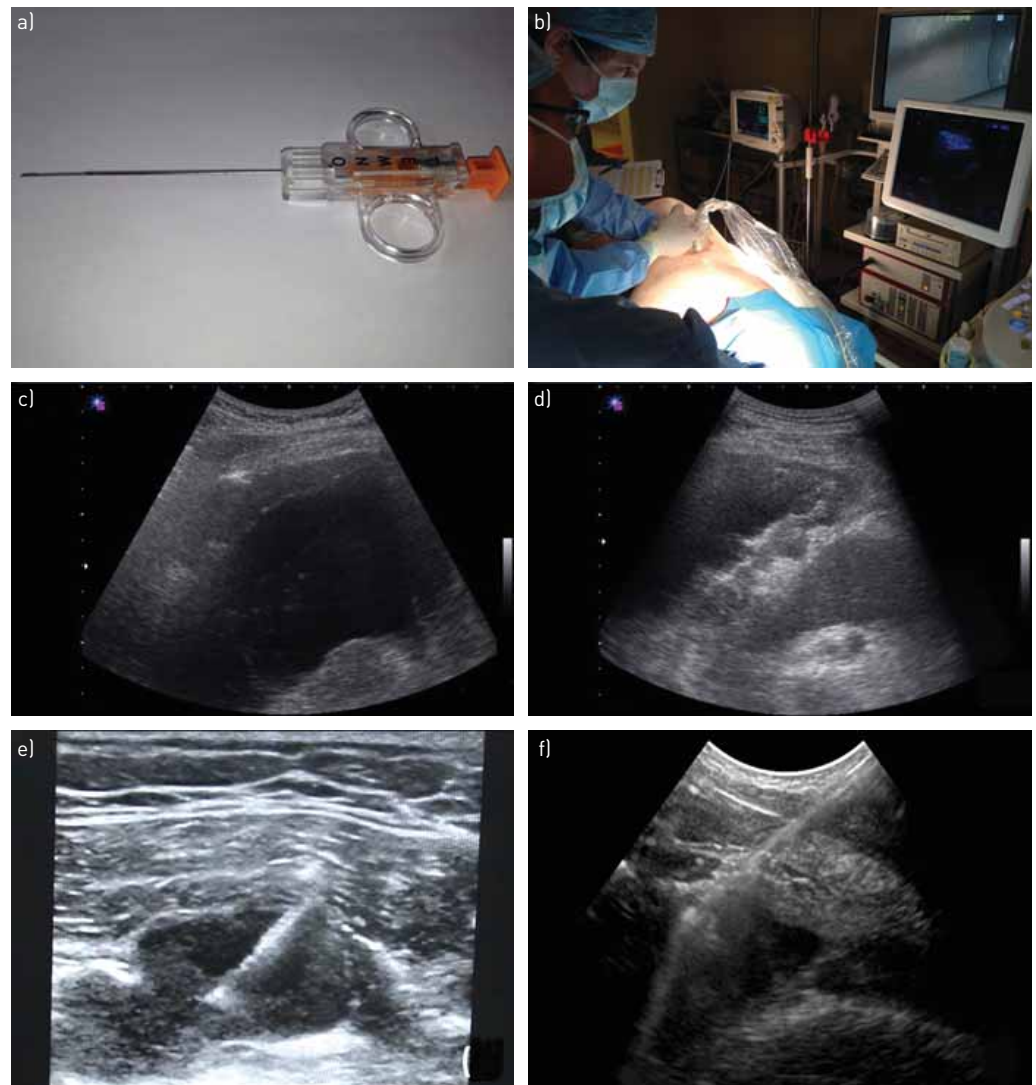


FIGURE 3 Closed pleural biopsy. a) Example of a core-biopsy cutting needle. b) Example of procedural room set-up with operator line of sight and in-plane real-time ultrasound guidance. c) Ultrasound view of irregular parietal pleural thickening with effusion. d) Ultrasound view of irregular diaphragmatic and parietal pleural thickening with effusion. e) High-frequency (10 MHz) real-time ultrasound-guided cutting needle biopsy of pleural and chest wall mass. f) Low frequency (3.5 MHz) real-time ultrasound-guided cutting needle biopsy of parietal pleural thickening.

impact negatively on those cases where additional molecular analysis is required or histological diagnosis can be particularly challenging (e.g. mesothelioma).

Medical thoracoscopy

The first published report of a thorascopic intervention dates back to 1866 when Cruise and GORDON [108] utilised a urological endoscope in the treatment of a pleural empyema at the Mater Misericordiae Hospital in Dublin, Ireland. However, it is JACOBÆUS [109, 110] who is widely regarded as the father of thoracoscopy, having published widely on the technique and its different indications over three decades in the early 20th century; in particular, the artificial induction of pneumothorax and division of pleural adhesions in order to treat tuberculosis. The discovery of antituberculous agents such as streptomycin in the 1950s led to a rapid decline in the use of thoracoscopy; it was not until the late 1980s when advances in miniature camera, fibreoptic and video technology allowed the technique to be revived. Thoracoscopy has grown steadily in popularity ever since, with both thoracic surgeons and pulmonologists offering the procedure due to its combined diagnostic and therapeutic capabilities.

Although a clear distinction should be made between medical thoracoscopy (*i.e.* physician-led procedures) and thoracic surgical intervention, it is important to recognise that interventional pulmonologists are performing increasingly complex thorascopic interventions, including those under general anaesthesia, on a regular basis. The available data suggest that medical thoracoscopy is a safe procedure with a mortality rate of <1%, generally associated with the use of insufflated talc as a therapeutic agent, and a low risk (<10%) of peri-procedural morbidity or complications [111].

Technical considerations

As outlined earlier in this review article, appropriate patient selection is critical prior to embarking on any interventional procedure. There are published guidelines addressing this subject area along with the facilities and support staff necessary to deliver a safe and efficient thoracoscopy service [111]. Although the majority of physicians perform thoracoscopy under local anaesthetic and analgesedation, it is worth noting that some larger specialist units also offer a general anaesthetic service that in turn facilitates more complex interventions. The presence of anaesthetic support also allows selective intubation and lung isolation, facilitating positive-pressure inflation of the collapsed lung under thorascopic vision prior to talc poudrage. This may allow the identification of NEL and contemporaneous insertion of an IPC to allow a single-step complete management strategy.

The choice of sedative agent(s) during thoracoscopy should be made on a case-by-case basis and determined by operator experience, patient characteristics and the nature of the procedure to be undertaken [112]. The patient is placed in the lateral decubitus position and a detailed ultrasound examination performed to determine both the underlying anatomy and point of access that will maximise the likelihood of procedural success [113, 114]. A trocar and port are introduced following blunt dissection of the chest wall (analogous to large-bore surgical chest drain insertion), usually in the fourth to sixth intercostal space between the mid- and anterior axillary line. The pleural fluid is then evacuated completely using a suction catheter before inserting the thoracoscope and inspecting the thoracic cavity thoroughly.

Successful thoracoscopy is dependent on having an adequate working space both to manipulate instruments and to allow full visualisation of the thoracic cavity, since abnormalities may be subtle and/or highly localised: early metastatic deposits frequently favour a posterobasal location and, consequently, the pleural space cannot be cleared without careful inspection of the paraspinal gutter and diaphragmatic recesses. Gaining access to the thoracic cavity is relatively straightforward in the context of a moderate to large pleural effusion; however, the absence of any pleural fluid should not be considered a barrier to medical thoracoscopy. Assuming significant pleural adhesions are excluded through the confirmation of lung sliding on ultrasound, pneumothorax induction can then be safely performed using either blunt dissection or Boutin needle introduction under real-time ultrasound visualisation [115, 116]. Following a complete inspection of the thoracic cavity, biopsies of the parietal pleura are then obtained; the authors would advise taking multiple biopsies from different sites to maximise the probability of a secure diagnosis. In the specific context of suspected mesothelioma with diffuse parietal pleural thickening on macroscopic inspection, deep “strip” biopsies should be obtained down to the level of periosteum in order to limit any diagnostic uncertainty on subsequent histological examination. Rapid on-site evaluation of thorascopic biopsies may reduce the likelihood of nondiagnostic interventions, as has been the case in endobronchial ultrasound and mediastinal node sampling [117], but as yet, there are no published data to support this conclusion (figure 4).

The majority of published data on medical thoracoscopy relate to procedures utilising a rigid thoracoscope. However, there is a growing body of interventional pulmonologists who favour a semirigid

instrument as a result of its increased flexibility, familiarity of use and compatibility with existing equipment due to the similarities with flexible bronchoscopes. There are limited data comparing the diagnostic yield of pleural biopsies taken using either a rigid or semirigid thoracoscope, although what has been published has not identified a significant difference between these techniques [118–119]. The authors tend to favour rigid thoracoscopy: besides the larger working channel and ability to obtain larger biopsies that this approach offers, there is also the option to convert to a two-port technique that facilitates more complex procedures such as extended adhesiolysis. Nonetheless, it is less of an issue whether a rigid or semirigid thoracoscopic approach is utilised, and more important that the procedure is done well and safely. With respect to this, there is no formal guideline available as yet that specifically details training standards for medical thoracoscopy; given its increasing use the development of this resource should be regarded as a priority in the near future [111, 121].

Undiagnosed pleural effusion and MPE

Medical thoracoscopy is well established as a key diagnostic test in the investigation of an exudative pleural effusion of unknown cause [30], with excellent sensitivity and specificity in both tuberculous and malignant effusions where previous less invasive investigations have failed to yield the diagnosis [111]. Up to a third of patients with an exudative effusion will be diagnosed with nonspecific pleuritis/fibrosis (NSP) on thoracoscopic biopsies; in these circumstances, the authors recommend a minimum of 2 years' clinical and imaging follow-up due to the risk of developing malignancy at a later stage (~10% of cases of NSP), particularly mesothelioma [4, 122, 123].

In contrast to techniques such as CPB or tube thoracostomy, thoracoscopy permits a combined diagnostic and therapeutic procedure. Complete drainage of large-volume effusions is feasible with a low risk of complications such as REPO [111, 124], facilitating an immediate pleurodesis. In physician-led procedures, this is most commonly performed using a poudrage of sterile graded large-particle talc. Whether this particular method of pleurodesis has a therapeutic advantage in established MPE over traditional talc slurry following tube thoracostomy remains unanswered by the currently available data [125, 126], although a large-scale RCT is currently underway with the aim of answering this important clinical question [127]. Some clinicians have proposed the placement of an IPC at the same time as thoracoscopy

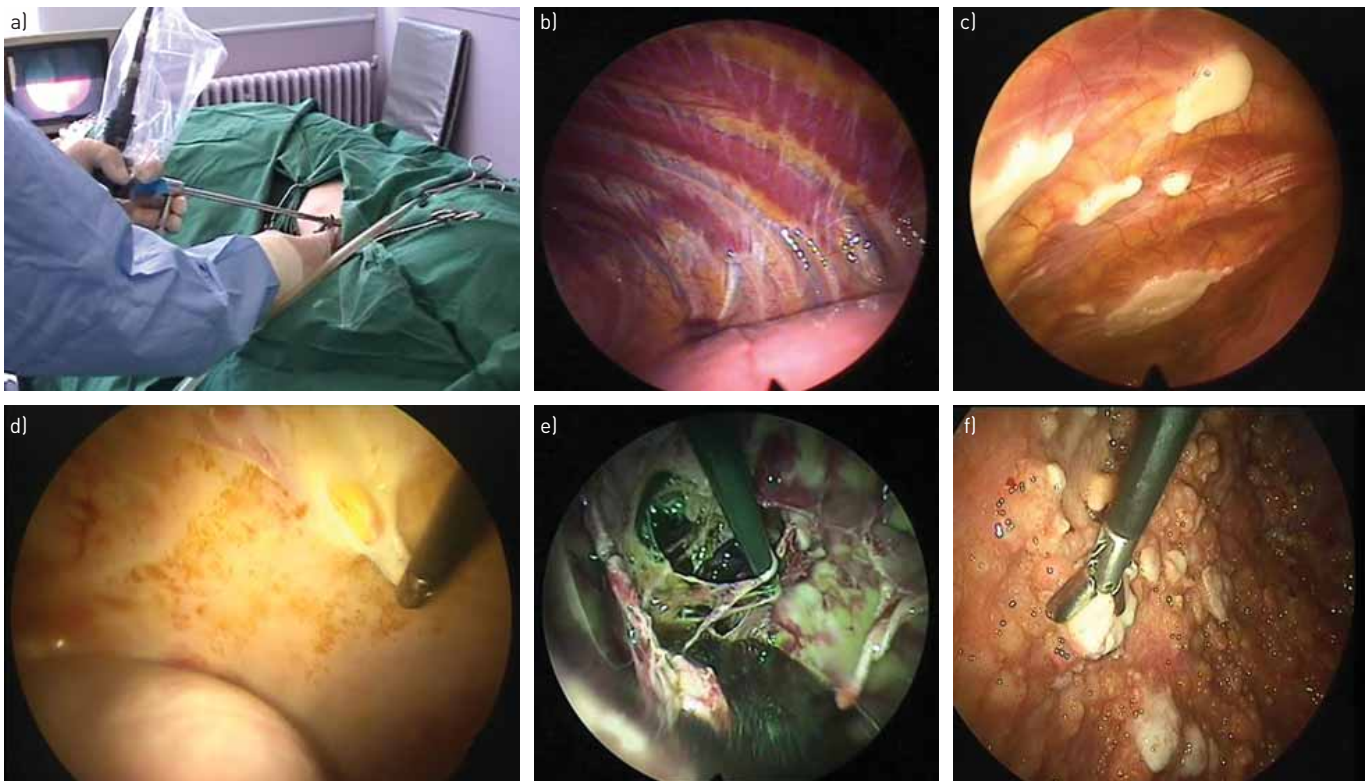


FIGURE 4 Medical thoracoscopy. a) Example of procedural room set-up for rigid thoracoscopy. b) Normal parietal pleura with clearly defined anatomy. c) Pleural plaque disease with typical “fried-egg” appearance overlying ribs. d) Diffuse parietal and visceral pleural thickening secondary to mesothelioma with two-port strip biopsy technique. e) Heavily septated pleural space using two-port technique to divide septations in context of intercurrent malignancy and infection. f) Widespread malignant pleural nodularity with two-port biopsy technique.

is performed, facilitating both early discharge from hospital and long-term fluid control in the event of pleurodesis failing and/or the underlying lung being trapped [128]. This particular strategy needs further evaluation to determine the benefits and risks to patients alongside its economic credibility.

The infected pleural space

The standard management of pleural infection is centred on appropriate antibiotic choice and adequate evacuation of infected material from the thoracic cavity, most commonly *via* tube thoracostomy with or without intrapleural fibrinolytic therapy [129]. In a significant minority of cases, this approach fails and a rescue procedure is required. Traditionally, this has been the domain of thoracic surgeons using either video-assisted thoracoscopic surgery or open thoracotomy to perform adhesiolysis, decortication and washout. However, there are published data describing the use of medical thoracoscopy in this clinical scenario, both as a rescue therapy where conservative measures have failed or as a front-line intervention aimed at improving clearance through adhesiolysis and targeted drain placement [130–132]. These studies are small and observational only, and a RCT addressing the potential role of early medical thoracoscopy in pleural infection is needed to provide a definitive answer.

Pneumothorax

Recurrence rates in primary and secondary spontaneous pneumothorax have been reported as being as high as 50% in some studies; since these rates increase after the first recurrence, definitive treatment is recommended in those patients who suffer a second episode [40, 133]. More invasive management may also be indicated after one episode in specific scenarios such as prolonged air leak or where occupational regulations demand early treatment (*e.g.* pilots) [133]. Once more, whilst this has conventionally been the realm of the thoracic surgeon, medical thoracoscopy has been successfully used to treat patients with spontaneous pneumothorax. A RCT comparing medical thoracoscopic talc poudrage with standard conservative pleural drainage in 108 patients with primary spontaneous pneumothorax demonstrated improved clinical and economic outcomes for those patients who underwent thoracoscopy [134]. A smaller prospective case series of 41 patients with secondary spontaneous pneumothorax also reported favourably with low rates of recurrence and peri-procedural morbidity and mortality [135]. Whilst there are as yet no head-to-head trials comparing differing thoracoscopic management of spontaneous pneumothorax, data suggesting pleurodesis may be the key therapeutic intervention, and that chemical pleurodesis is equivalent to either mechanical abrasion and/or pleurectomy would appear to indicate a potential role for medical thoracoscopy in selected cases [136–138].

Other conditions

There are limited data relating to the use of medical thoracoscopy in the diagnosis and treatment of other conditions including recurrent symptomatic benign effusions, notably hepatic hydrothorax [139–141], sympathectomy for palmar hyperhidrosis [142, 143], and forceps lung biopsy for suspected interstitial lung disease [144]. Whilst these are worth mentioning as areas that might be explored further in future studies, thoracic surgeons continue to perform the majority of these procedures and there is no current evidence to suggest a definitive role in routine clinical practice for the interventional pulmonologist.

Future directions

The field of interventional pulmonology is continuing to grow and advance rapidly, with changes in the diagnosis and management of pleural disease at the forefront of these changes. The recognition of pleural disease as a distinct subspecialty within respiratory medicine has been central to this, and the next few years are likely to see an increasing number of centres offering rapid access clinics and procedural lists focused on diagnosis, treatment and outpatient management for this patient population [1, 145]. In some respects, the early expansion of this field and, in particular, the delivery of interventional services has been driven by individual enthusiasts at a local level. However, with advanced interventions such as medical thoracoscopy and CPB being incorporated into guidelines as standard practice, the development of robust training standards to be applied on a national and international basis must be a priority [121]. Previously published guidelines [111, 146] are becoming progressively more outdated, and have been outstripped by the surge of interest in and provision of these services by physicians. It is consequently time for experts in the field to ensure that training and clinical practice are standardised with robust assessment and audit methodology to maintain a high and uniform level of care for patients.

Looking beyond the currently recruiting studies already outlined above that are expected to influence patient care within the next few years, there are a number of outstanding research questions still to be addressed. Developing the ambulatory day-case pathway for patients with pleural disease is one such area. IPCs have revolutionised outpatient management of recurrent symptomatic MPE; similarly, portable devices are being evaluated in the treatment of spontaneous pneumothorax, whilst the question of whether

patients with pleural infection stratified as low risk [147] could be cared for on an outpatient basis with intermittent therapeutic thoracentesis or ambulatory drainage is still unanswered almost two decades after its initial proposal [148]. Even a significant intervention such as medical thoracoscopy may be feasible on a day-case basis in a carefully selected subset of patients [149]; its combination with IPC insertion for patients confirmed as having malignant pleural disease may provide a complete outpatient service without the need for even a single overnight stay in hospital [128].

As the expertise of interventional pulmonologists with thoracoscopy improves, it is likely that new techniques and indications for diagnostic and therapeutic procedures will be identified. A recently described novel three-dimensional thorascopic camera [150] may improve diagnostic yield and accessibility in patients with highly localised pleural disease. The use of semirigid thoroscopes is becoming more common, although one criticism frequently raised is whether they permit sufficient diagnostic tissue to be obtained in cases where the parietal pleura is diffusely thickened and resistant to sampling. This might be overcome by cryoprobe biopsy [151, 152], although the routine use of this technique needs evaluation as part of a prospective multicentre trial. There have also been reports of the use of narrow-band imaging [153] and autofluorescence [154–156] during thoracoscopy as a means of identifying malignant change in the parietal pleura that is not otherwise macroscopically evident under white light inspection. Although promising, both of these remain techniques without a disease as long as it is unclear whether they can influence key clinical outcomes; in particular, the identification of patients who might otherwise be given a false-negative diagnosis of NSP.

Conclusion

With technological advances and greater availability of the techniques described in this article, the interested respiratory physician can now lay claim to a broader range of skills than at any other time, even those which may have previously been considered as uniquely radiological or surgical. For those wishing to focus on advanced pleural procedures, however, there is perhaps now a greater responsibility than ever before. Once skills are learned, there is a requirement to maintain and, if possible, improve standards, but perhaps more importantly, there must be recognition of the limits of one's own capabilities so as not to expose patients to unnecessary risk. Nonetheless, these are exciting times for both pulmonology as a whole and for pleural interventional practice specifically. Practitioners are now able to offer more to patients than ever before and, from a patient's perspective, this is ideal, limiting the need for repeated referrals, and both expediting and simplifying the often confusing journey towards diagnosis and treatment.

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